Supplementary Material

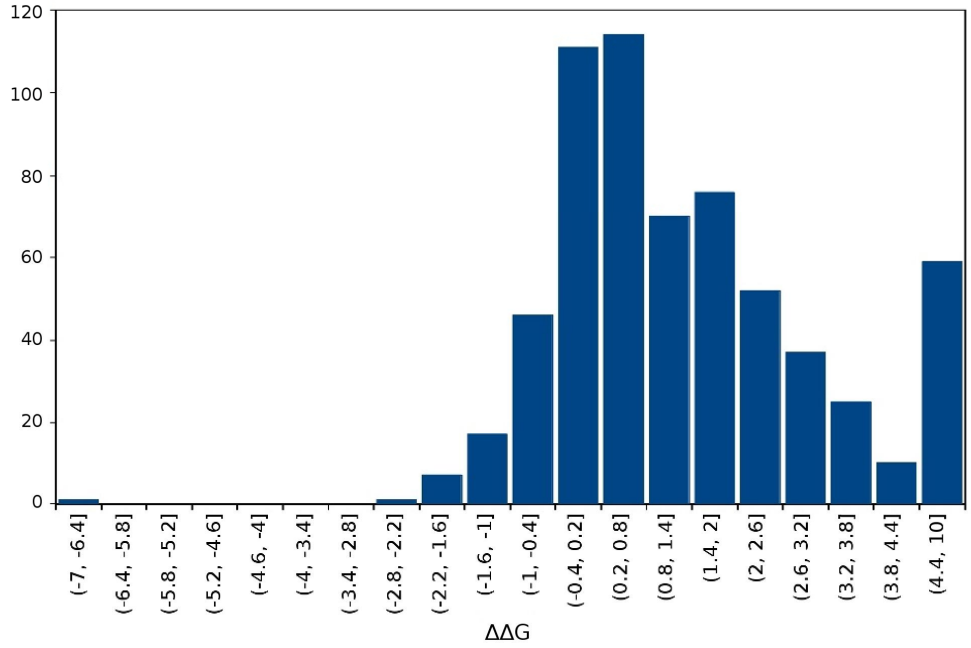

Figure S1. qpG distribution on the IM_631 dataset.

Feature	Description
Residue ID	The one-hot encode of the (1) mutant amino-acid (2) for the following, (3) the previous position in the sequence and the (4) wild type residue.
Neighbor residues	The frequency of the residues within a 5 Angstrom radius from the mutant amino-acid. Therefore, a vector store the number of observations for each of the 20 possible residues in this sphere.
Secondary structure	The one-hot encode of the secondary structure for the (1) mutant residue, (2) for the following, and (3) the previous position in the sequence. Secondary structure can be classified as *alpha*, *beta* or *coil*.
Solvent Accessibility	The Solvent Accessibility calculated by DSSP for the (1) mutant residue, (2) for the following, and (3) the previous position in the sequence.
Conservation	The conservation for the (1) mutant residue, (2) for the following, and (3) the previous position in the sequence. It is calculated using PSI-BLAST on the UniRef90 database.
Mutual information	The mutual information for the (1) mutant residue, (2) for the two following, and (3) the two previous position in the sequence. This is measure of mutual dependence of two variables X and Y. It is defined as follows: $$MI(X,Y) = \sum_{x \in X} \sum_{y \in Y} p(x,y) \log \frac{p(x,y)}{p(x)\,p(y)}$$
Average Cluster Purity	The Average Cluster purity for the (1) mutant residue, (2) for the two following, and (3) the two previous position in the sequence. This measure is used in general to evaluate the classification performances of clustering algorithms. It is defined as follows: $$ACP = \frac{1}{N} \sum_{i=1}^{N_p} \sum_{j=1}^{N_c} \frac{n_{ij}^2}{n_i}$$ where N_p is the number of clusters that we are considering, N_c is the number of classes in our dataset, n_i is the size of the i-th cluster, n_{ij} is the amount of elements of class j that belong to cluster i and N is the number of samples. Clearly, in RING this is used to evaluate the different distribution of amino-acids in two sequence positions.
Torsion angle potential (TAP)	The torsion angle potential as defined in [23] for the (1) mutant residue, (2) for the following, and (3) the previous position in the sequence.
FRST potential	The overall FRST potential defined in [24] for (1) mutant residue, (2) for the following, and (3) the previous position in the sequence.
QMEAN potentials	The nine potentials defined in [25] for the (1) mutant residue, (2) for the following, and (3) the previous position in the sequence: • all atom pairwise energy window (two windows size) • all atom pairwise energy window considering the secondary structure (two windows size) • C-beta pairwise energy window • C-beta pairwise energy window considering the secondary structure • Torsion energy window • Combined torsion energy window • C-beta solvation energy window

	QMEAN is a well-known tool used for protein modeling assessment. All its potentials are used in our context to evaluate the geometrical aspects of a protein structure.
Network centralities	Seven different node centralities for the (1) mutant residue, (2) for the following, and (3) the previous position in the sequence. Basically, all these measures evaluate either the localization of the node in the network (if it is in the neighborhood or in the center) or the importance of the node for the connectivity of the graph: • node eccentricity • clustering coefficient • neighborhood connectivity • stress centrality • closeness centrality • betweenness centrality • node radiality All those measures are defined in [NetworkAnalyzer]. They are computed for all the sub-networks produced by RING, which distinguish: • hydrogen bond network • inter-atomic contact network • pi-cation interaction network • pi-pi interaction network • ionic interaction network • disulfide interaction network • main chain-main chain interactions • main chain-side chain interactions • side chain-side chain interactions • the union of all networks
PH and temperature	The context where the mutation should be evaluated
Length	The length of the protein

Table S1. Description of the features used in NeEMO.

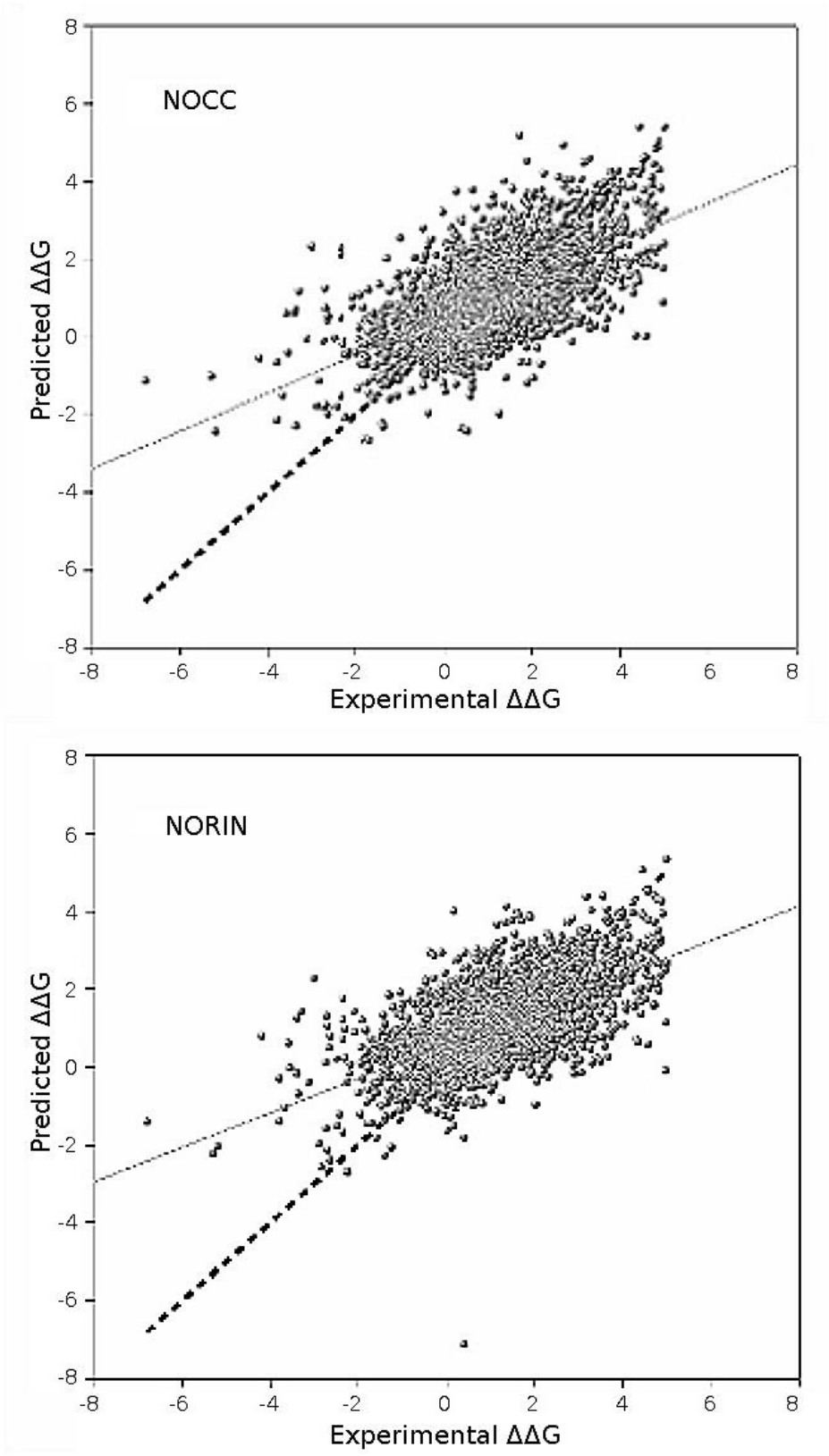

Figure S2. Regression of the experimental data on NeEMO different neural network.

Ŭhelices		*r*		*ɟ*		*Ű*	
Method	**Mutations**	**Method**	**NeEMO**	**Method**	**NeEMO**	**Method**	**NeEMO**
Auto-Mute	426	**0.737**	0.591	**0.712**	0.58	**0.539**	0.408
I-Mutant 2.0	804	**0.716**	0.658	**0.672**	0.625	**0.519**	0.446
I-Mutant 3.0	763	0.616	**0.664**	**0.653**	0.634	**0.461**	0.453
MuPro	857	**0.658**	0.644	**0.612**	0.611	**0.455**	0.435
PoPMuSiC 2.0	858	0.614	**0.645**	**0.627**	0.612	**0.451**	0.436

Table S2. Correlation measures computed on mutations occurring only in Ŭhelices on the 10 fold cross-validation training dataset.

ɓ strands		*R*		*ɟ*		*Ű*	
Method	**Mutations**	**Method**	**NeEMO**	**Method**	**NeEMO**	**Method**	**NeEMO**
Auto-Mute	359	0.655	**0.705**	0.666	**0.691**	0.482	**0.51**
I-Mutant 2.0	662	0.63	**0.731**	0.647	**0.692**	0.469	**0.511**
I-Mutant 3.0	687	0.706	**0.729**	0.675	**0.707**	0.467	**0.523**
MuPro	784	0.608	**0.716**	0.618	**0.687**	0.438	**0.506**
PoPMuSiC 2.0	784	0.68	**0.716**	0.663	**0.687**	0.487	**0.506**

Table S3. Correlation measures computed on mutations occurring only in ɓ strands on the 10 fold cross-validation training dataset.

Coil		*r*		*ɟ*		*Ű*	
Method	**Mutations**	**Method**	**NeEMO**	**Method**	**NeEMO**	**Method**	**NeEMO**
Auto-Mute	359	**0.651**	0.565	**0.644**	0.573	**0.487**	0.404
I-Mutant 2.0	705	0.535	**0.594**	0.522	**0.601**	0.394	**0.426**
I-Mutant 3.0	662	0.489	**0.587**	0.550	**0.59**	0.385	**0.42**
MuPro	757	0.541	**0.581**	0.466	**0.588**	0.344	**0.418**
PoPMuSiC 2.0	757	0.508	**0.581**	0.517	**0.588**	0.365	**0.418**

Table S4. Correlation measures computed on mutations occurring only in coil conformation on the 10 fold cross-validation training dataset.

Exposed (RSA >25%)		*r*		*ɟ*		*Ű*	
Method	**Mutations**	**Method**	**NeEMO**	**Method**	**NeEMO**	**Method**	**NeEMO**
Auto-Mute	495	**0.689**	0.588	**0.672**	0.567	**0.506**	0.404
I-Mutant 2.0	980	**0.637**	0.614	**0.564**	0.561	**0.426**	0.399
I-Mutant 3.0	925	0.553	**0.617**	**0.618**	0.556	**0.430**	0.395
MuPro	1039	**0.620**	0.603	0.527	**0.551**	**0.394**	0.391
PoPMuSiC 2.0	1039	0.571	**0.603**	**0.572**	0.551	**0.405**	0.391

Table S5. Correlation measures computed on mutations occurring only on exposed residues (e, RSA > 25%) on the 10 fold cross-validation training dataset.

Buried (RSA Ò25%)		*r*		*ɟ*		*Ű*	
Method	**Mutations**	**Method**	**NeEMO**	**Method**	**NeEMO**	**Method**	**NeEMO**
Auto-Mute	649	**0.652**	0.609	**0.653**	0.591	**0.474**	0.421
I-Mutant 2.0	1191	0.588	**0.647**	0.583	**0.616**	0.428	**0.442**
I-Mutant 3.0	1187	0.630	**0.653**	0.611	**0.635**	0.424	**0.458**
MuPro	1359	0.579	**0.638**	0.567	**0.614**	0.405	**0.440**
PoPMuSiC 2.0	1360	0.581	**0.638**	0.548	**0.614**	0.393	**0.441**

Table S6. Correlation measures computed on mutations occurring only on buried residues (b, RSA Ò25%) on the 10 fold cross-validation training dataset.